

R E M A R K S

This paper is submitted to respond to the issues presented in the Office Action of April 12, 1989, in applicant's parent patent application, U. S. Serial No. 231,217, filed August 11, 1988. The parent application is being abandoned without prejudice in favor of the instant patent application.

Claim 1 of the parent patent application was rejected under 35 USC 112, second paragraph. Specifically, the language "invasive or noninvasive techniques" was objected to as presenting "improper alternatives". Note that this language does not appear in the newly submitted claims and this rejection is inapplicable.

Claims 12 and 13 to perfusion imaging are generic to noninvasive techniques. Claim 14 is generic to invasive technique since the means for measuring coronary blood flow necessarily involves the use of a coronary catheter or similar invasive procedure.

By this letter, it is applicant's hope that the examination of this patent application can be brought to a conclusion with a minimum of delay.

The claims of the parent patent application were rejected on Crystal et al., "Small Volume and Total Coronary Blood Volume During Intracoronary Adenosine", American Journal of Physiology, 241 (2), 1981, pages 194-201, paper alone, or as to claims 11 and 12, in conjunction with Camici et al., "A Multitracer Autoradiographic Technique For Imaging Myocardial Flow and Metabolism", Conference: Computers in Cardiology, 1981, pages 159-162.

Crystal et al conducted a study limited to dogs which showed that adenosine infused into the coronary artery (intracoronary) caused dilation of the large vessels (larger than 100 μ m diameter), but did not dilate the smaller or capillary vessels. It is known in the art that results in a dog model do not predict results in other animal species or in man. History is replete with cases wherein drugs worked in animals but were not efficacious in man or proved to be toxic to man. This is particularly true in the case of adenosine where adenosine receptor differences between species preclude prediction of the therapeutic and/or diagnostic effect in man.

Crystal et al states that in his study, there was a sixfold increase in myocardial blood flow. Crystal et al speculates that if myocardial blood flow were held constant, or under conditions of increased coronary oxygen consumption, adenosine might also dilate the smaller coronary cap-

illaries. The fact that a drug is a coronary vasodilator does not mean that the drug has a benefit in cardiac imaging, viz, nitrates and calcium channel blockers are coronary vasodilators but have no role in cardiac imaging.

There is no indication that any of the subject dogs in Crystal et al had coronary artery disease. Therefore, one can assume that they were healthy animals without previously documented evidence of coronary artery disease. Crystal et al does not disclose anything regarding the effects of adenosine on diseased coronary arteries in dogs. It is only in the presence of a physiologically significant coronary stenosis that adenosine produces the perfusion mis-match necessary for successful diagnostic non-invasive cardiac imaging. Furthermore, it is only in the presence of a physiologically significant coronary stenosis that adenosine produces a disparity in coronary blood flow velocity necessary for successful diagnostic invasive cardiac imaging.

The results of Crystal et al do not suggest the effect of adenosine on humans having coronary artery disease, and consequently Crystal et al does not suggest the diagnostic use of adenosine in the detection of the presence and extent of coronary artery disease in humans. The diagnostic value of adenosine can only be determined based on information from human studies relating to its sensitivity (ability to

detect disease) and specificity (ability to detect normalcy) of the condition for which it is being utilized.

The diagnostic use and value of adenosine as described in this patent application has not been previously reported. This value and use was not obvious despite the fact that adenosine has long been known to be a coronary vasodilator, and that various other coronary vasodilators such as papavarine have been used for this purpose.

The applicants' preferred procedure involves the administration of the drug by intravenous infusion. Crystal et al administered adenosine to dogs by the intracoronary route which is not predictive of the use when the drug is administered by the intravenous route. For example, papavarine is widely used by the intracoronary route, but has been proven not to be useful when given intravenously.

Adenosine and related compounds possess several advantages over the other synthetic agents such as, nitrates, papavarine, and dipyridamole. First, adenosine has a direct mode of action at the adenosine receptor site which results in the more predictable dose response than is the case with papavarine or dipyridamole. Adenosine is also the most potent available coronary vasodilator, a property which is highly advantageous in producing optimal cardiac imaging. Thirdly, adenosine has an ultra short half-life (one to two

seconds), unlike nitrates (four minutes), papavarine (six hours) and dipyridamole (ten hours). As a result, adenosine's onset of action and clearance from the body is rapid and consequently the time required to perform the diagnostic procedure is shortened. Furthermore, side effects when they occur are mild, and transient, and in most cases are rapidly resolved when the infusion is terminated. In addition, in the isolated case where adenosine discomforts persist, if they persist, can be easily and successfully treated with theophylline or another adenosine antagonist. Still further, adenosine is an endogenous substance in humans and is not known in humans to result in allergic reactions. In light of the advantages of adenosine over the synthetic compounds previously used in the detection and evaluation of coronary artery disease, it is quite clear that the use of adenosine for this purpose was not obvious to those skilled in the art.

Camici et al is limited to a discussion of several radio labelled reagents for myocardial imaging. Camici et al has no direct relevance to the subject matter of this patent application.

The Examiner also cited, but did not rely upon:

U. S. Patent No. 4,709,703 Lazarow et al

U. S. Patent No. 4,689,041 Corday et al

Kwan et al., "Photoaffinity of adenosine transporter in cardiac membranes with nitrobenzylthiosine," Am J Physiol 246(5), 1984, 710-715.

Hayden et al., "Scintiphotographic Studies of Acquired Cardiovascular Disease", Nuclear Medicine, Vol. 3, No. 2, 1973, 177-190.

We have considered these citations and they are not pertinent. Lazarow et al refers briefly to the intracoronary delivery of adenosine solution to dilate one of the descending coronary arteries in dogs. We are unable to speculate as to the reason for the citation of Corday et al. Adenosine is not referred to in this patent.

Kwan et al pertains to an in vitro study using guinea pig heart membranes. This study is of no apparent relevance to the present patent application.

Hayden et al discusses several angiography studies where the imaging agent is Tc⁹⁹-- pertechnetate. This paper is not pertinent to the present invention.

In the absence of pertinent prior art, the Notice of Allowance is requested.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "J E Mueth", with a long horizontal flourish extending to the right.

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